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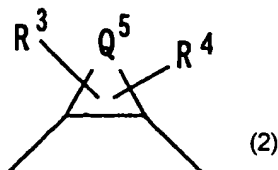
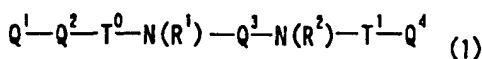
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[続葉有]

(54) Title: DIAMINE DERIVATIVES

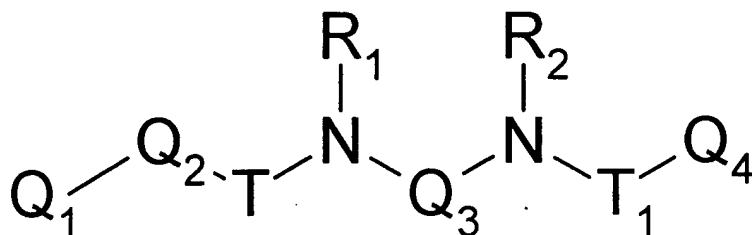
(54) 発明の名称: ジアミン誘導体



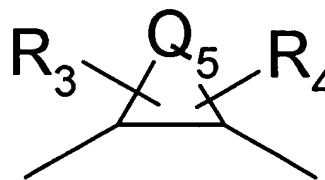
(57) Abstract: Compounds represented by the following general formula (1), salts thereof, solvates of the same or N-oxides of the same: $Q^1-Q^2-T^0-N(R^1)-Q^3-N(R^2)-T^1-Q^4$ (1) wherein R^1 and R^2 represent each hydrogen, etc.; Q^1 represents optionally substituted, saturated or unsaturated 5- or 6-membered hydrocarbyl, etc.; Q^2 represents a single bond, etc.; Q^3 represents the following group; (wherein Q^5 represents C_{1-8} alkylene, etc.); and T^0 and T^1 represent each carbonyl, etc. These compounds are useful as preventives and/or remedies for brain infarction, cerebral embolism, myocardial infarction, angina, pulmonary infarction, pulmonary embolism, Buerger's disease, bottom venous thrombosis, disseminated intravascular coagulation, thrombosis following artificial valve/joint replacement, thrombosis and reocclusion following circulation reconstruction, systemic inflammatory responsive syndrome (SIRS), multiple organ dysfunction (MODS), thrombosis in extracorporeal circulation or blood coagulation in collecting blood.

[続葉有]

L7 ANSWER 2 OF 3 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
 AN 2003-247888 [24] WPIX Full-text
 CR 2003-247714 [24]; 2003-256264 [25]; 2003-312743 [30]
 TI New diamine compounds are activated blood factor X inhibitors used for
 treating e.g. cerebral or myocardial infarction and angina.
 PA (DAUC) DAIICHI PHARM CO LTD
 PI WO 2003000680 A1 20030103 (200324)* JA 811 C07D401-12 <--
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
 EP 1405852 A1 20040407 (200425) EN C07D401-12
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
 PRAI WO 2002-JP2683 20020320; JP 2001-187105 20010620;
 JP 2001-243046 20010809; JP 2001-311808 20011009;
 JP 2001-398708 20011228
 TECH UPTX: 20030410



(I)



(i)

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I; T = C(O)) Are
 prepared e.g. by reacting an amine of formula (IV) with an acid of formula (V).
 AB WO2003000680 A UPAB: 20040418
 NOVELTY - Diamine compounds (I) are new.
 DETAILED DESCRIPTION - Diamine compounds of formula (I) and their salts, solvates and N-oxides
 are new. R1, R2 = H, OH, alkyl or O-alkyl; Q1 = 5-6C carbocyclyl, 5-7 membered heterocyclyl
 or bi- or tri-cyclic carbocyclyl or heterocyclyl (all optionally unsaturated and optionally
 substituted);
 Q2 = a bond, or divalent 5-6C carbocyclyl, 5-7 membered heterocyclyl or bi- or tri-cyclic
 carbocyclyl or heterocyclyl (all optionally unsaturated and optionally substituted); Q3 = a
 group of formula (i);
 Q5 = 1-8C alkylene, 2-8C alkenylene or (CH2)mCH2ACH2(CH2)n; m, n = 0-3;
 A = O, N, S, SO, SO2, NH, ONH, NHH, SNH, SONH or SO2NH; R3, R4 = H, OH, alkyl (optionally
 substituted by CN, NH2, NHA, NAA, acyl, acylamino, O-alkyl, OH, COOH, COOalk, NHCOOA, N-
 alkenylcarbamoyl, N-alkenyl-N-alkyl-carbamoyl, CONHO-alkyl, CON(A)OA, SO2A, CONH2, OCONH2,
 OCONHA, OCONAA, OCOHet, COHet, Ar1, NHSO2-alkyl, NHSO2Ar, CONHSO2-alkyl, CONHSO2Ar or
 optionally substituted CONHA or CONAA), alkenyl, alkynyl, halo, acyl, optionally substituted
 acylamino, O-alkyl, COOH, COO-alkyl, NHACOOA, NHACOOH, CONH2, CONHA, CONAA, N-
 alkenylcarbamoyl, N-alkenyl-N-alkyl-carbamoyl, CONHO-alkyl, CON(A)OA, CON(A)3, SO2A, COHet,
 Ar1, NHSO2-alkyl, NHSO2Ar, CONHSO2-alkyl, CONHSO2Ar, oxo, OCONH2, aralkoxy, O-alkyl-COOH,
 acyloxy, SO2Ar, SO2-alkyl-COO-alkyl, SO2-alkyl-COOH, acyl substituted by COO-alkyl, OH, O-
 alkyl, halo, COOH, NH2, acyloxy, NH-alkyl, N(alkyl)2, SO2-alkyl or optionally substituted
 CON(alkyl)2, COO-alkyl-O-alkyl or acyloxyalkylsulfonyl, SO2-alkyl-OH, SO2O-alkyl, SO2Het or
 optionally substituted SO2CON(alkyl)2, or R3 + R4 = 1-5C alkylene, 2-5C alkenylene, 1-5C
 alkyleneoxy or carbonyldioxy;
 Het = optionally substituted 3-6C heterocyclyl; Ar1 = aryl or heteroaryl;
 Ar = aryl;

Q4 = Ar1, arylalkenyl, arylalkynyl, heteroarylalkenyl or optionally unsaturated bi- or tri-cyclic carbocyclyl or heterocyclyl (all optionally substituted);

T = CO or CS;

T1 = CO, SO2, COCONR11, CSCONR11, COCSNR11, CSCSNR11, COA1NR12, CONH, CSNH, CONHNNH, COA2CO, COA3CONH, C(=NORa)NRb, CS(=NORa)NRbCON=N, CSN=N, C(=NORc)CONRd, C(=NnReRf)CONRg or CS; R11, R12, Rb, Rd, Rg = H, OH, alkyl or O-alkyl; A1 = optionally substituted 1-5C alkylene; A2 = a bond or A1;

Ra = H, alkyl or alkanoyl;

Rc = H, alkyl, CO-alkyl, Ar or aralkyl, and Re, Rf = H, alkyl, CO-alkyl or CS-alkyl. ACTIVITY - Cerebroprotective; Anticoagulant; Cardiant; Antianginal; Respiratory; Anticoagulant; Thrombolytic; Vasotropic; Antiinflammatory.

MECHANISM OF ACTION - Factor X Inhibitor. In tests on rats, administration of N1-(4-chlorophenyl)-N2-((1S,2R,4S)-4-((dimethylamino)carbonyl)-2-(((5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridin-2-yl)carbonyl)amino)cyclohexyl)ethanediamide (Ia) (10 mg/kg orally) reduced blood FXa levels over 4 hours by 62-96 %.

USE - Used for treating and preventing e.g. cerebral infarction, cerebral embolism, myocardial infarction, angina, pulmonary, embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation, thrombosis following artificial flap/hip replacement or during external circulation, reocclusion, systemic inflammatory reaction syndrome, multiple organ failure or blood coagulation during blood collection.

ABEX

UPTX: 20030410

ADMINISTRATION - Administration of (I) is 0.1-200 (preferably 0.5-100) mg/kg/day orally or by injection.

EXAMPLE - 1-Hydroxybenzotriazole monohydrate (71 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloric acid (100 mg) were added to N-((1Rasterisk,2Sasterisk)-2-aminocyclopropyl))-5-chloroindole-2-carboxamide (108 mg) and lithium 5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridine-2-carboxylate (124 mg) in dimethylformamide (3 ml) and the mixture was stirred at room temperature for 8 hours. Work-up including silica gel chromatography (methylene chloride:methanol = 10:1) gave 72 mg of N-((1Rasterisk,2Sasterisk)-2-(((5-chloroindol-2-yl)carbonyl)amino)cyclopropyl))-5-methyl-4,5,6,7-tetrahydrothiazolo(5,4-c)pyridine-2-carboxamide hydrochloride.